REMARKS

Claims 5-7 and 19-29 are pending and under examination in the above-identified application. Applicant has review the rejections set forth in the Office Action mailed August 26, 2003, and respectfully traverse all grounds for the reasons that follow.

Rejections Under 35 U.S.C. § 112

Claims 5-7 and 19-29 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly lacking written description of the probes used in the claimed method for determining an IBD or pre-IBD phenotype. The Office asserts that the application fails to recite or give examples of identified up or down regulated IBD genes or the probes generated from the genes allegedly because the IBD gene set described in Table 1 is not directly used in the claimed invention. Table 1 is further alleged to lack sufficient description of nucleic acid probes allegedly because if fails to describe probe sequences, lengths or percent homology to the genes set forth therein. Relying on *Regents of Univ. of California v. Eli Lilly* the Office concludes that without knowing the probes, or nucleic acid sequences, used in the invention "it is impossible to practice the claimed method [and the] description is hypothetical." Office Action mailed February 13, 2004, at pages 3, 4, 9.

The written description requirement of § 112, first paragraph is satisfied when the applicant has conveyed to those skilled in the art that he or she was in possession of the invention as of the filing date of the application. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-1564 (Fed. Cir. 1991); *accord The Regents of the University of California v. Eli Lilly and Company*, 119 F.3d 1559, 1566 (Fed. Cir. 1997). As set forth in its previous response and further below, Applicant has satisfied this standard.

The claimed invention is directed to a method for determining an IBD or pre-IBD phenotype of a test cell from a given tissue. The method includes detecting the presence or absence of differential expression of at least 5 different genes shown in Table 1. The application describes 146 genes that are up- or down-regulated in intestinal cell samples from patients diagnosed with Crohn's disease (CD) and ulcerative colitis (UC), two types of inflammatory bowel disease (IBD). For example, the application describes:

> Genes showing three-fold or greater changes in expression levels were assigned to seven functional classes as indicated in Table 1.

Application at page 6, lines 27-28.

The application further describes:

> Table 1 indicates those sequences which are over- or underexpressed in a CD- or UC-derived cells [*sic*] relative to normal tissue.

Application at page 19, lines 6-7.

The application additionally describes that the:

> Subject polypeptides of the present invention include polypeptides encoded by the nucleic acids of Table 1.

Application at page 34, lines 24-25.

Beginning at page 51, Table 1 describes 146 different IBD genes that are up- or down-regulated. Described therein is the direction and fold change, indicated by an arrow and number (columns 2 and 3), the name of the gene (column 5), the sequence of the gene (column 4) and the functional category of the gene (column 1). Because Table 1 describes 146 genes that are up- or down-regulated Applicant has provided sufficient written description for detecting the presence or absence of at least 5 different genes shown in Table 1 as claimed by the invention.

The assertion that the IBD gene set described in Table 1 fails to provide adequate written description because the described genes are not directly used in the claimed invention is unsupported by the language of the claims. Initially, Applicant notes that the Office contradicts itself because under the § 103 rejections, the Office Action states:

> Applicants in the specification disclose the Genbank accession numbers of the genes <u>used</u> in the claimed method.

Office Action at page 6, paragraph 2 (emphasis added), *see also* Office Action at page 7, paragraph 2, lines 11-12 ("[t]he reference clearly do[es] not recite the genes or probes used in the method [of the invention]"). If this § 112, first paragraph rejection is maintained, Applicant respectfully requests that the Office clarify and provide its reasoning whether the genes set forth in Table 1 are or are not used in the claimed invention.

Further, Applicant claims detecting at least 5 different genes shown in Table 1. Because Applicant claims detecting genes in Table 1 and because at least 5 genes are set forth in

Table 1, the application provides express written description for this element as it is claimed in the invention.

While not conceding that the detection step is solely directed to detection by hybridization probes, the application, including Table 1, provides sufficient written description to satisfy the requirements of § 112, first paragraph. The application describes:

> In general, the subject IBD probes will be isolated nucleic acids (oligonucleotides) comprising a nucleotide sequence which hybridizes under stringent conditions to a sequence of Table 1 or a sequence complementary thereto. In a related embodiment, the nucleic acid is at least about 80% or about 100% identical to a sequence corresponding to at least about 12, at least about 15, at least about 25, or at least about 40 consecutive nucleotides up to the full length of one of the IBD gene set (see Table 1) or a sequence complementary thereto or up to the full length of the gene of which said sequence is a fragment.

Application at page 3, lines 26-32.

Therefore, the application describes that the genes set forth in Table 1 can be used as probes for detecting the at least 5 different genes shown in Table 1. The application further describes that the probe sequences can be at least about 80% or about 100% identical to a sequence set forth in Table 1 or its complement. Exemplary sizes of probes of the genes set forth in Table 1 also are described.

Table 1 additionally describes the sequences of the 146 IBD genes set forth therein. Column 4 of Table 1 provides the Genbank accession number for each of the described 146 IBD genes. The Genbank accession number provides adequate written description to show that applicant was in possession of the invention as claimed because the accession number provides a publicly available deposit of the nucleotide sequence of the gene.

Deposit of an organism, even in the absence of nucleotide sequence information, has been held to provide adequate written for probes hybridizing to the deposited organism. *Enzo Biochem, Inc., v. Gen-Probe, Inc.* (*Enzo Biochem II*), 323 F.3d 956, 967-68 (Fed. Cir. 2002). The Federal Circuit reasoned:

> [T]he sequences of the genomic DNA of those bacteria are not disclosed, perhaps because such sequencing would have been unduly burdensome at the time of Enzo's invention. . . . However, as those bacteria were deposited, their bacterial

> genome is accessible and, under our holding today, they are adequately described in the specification by their accession numbers. Because the claimed nucleotide sequences preferentially bind to the genomic DNA of the deposited strains of *N. gonorrhoeae* and have a complementary structural relationship with that DNA, those sequences, under the PTO Guidelines, may also be adequately described.

Id. (emphasis added); *accord Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F. 3d 1313, 1332 (Fed. Cir. 2003) (stating that *Enzo Biochem II* "clarified that *Eli Lilly* did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement); *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1320 (Fed. Cir. 2003) (emphasizing that written description was satisfied in *Enzo Biochem II* where "neither the specification nor the deposited biological material recited the precise "structure, formula, chemical name, or physical properties"'); *Noelle v. Lederman*, 355 F.3d 1343, 1349 (Fed. Cir. 2004) (reaffirming that *Enzo Biochem II* held that "one might comply with the written description requirement by depositing the biological material with a public depository"), and *University of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 925 (Fed. Cir. 2004) (observing that *Enzo Biochem II* explained that functional descriptions of genetic material can meet the written description requirement, reasoning that because it may be "a routine matter to envision the precise sequence of a 'complementary' strand . . . disclosure of a DNA sequence might support a claim to the complementary molecules that can hybridize to it").

The subject application satisfies the written description requirement of *Lilly* and its progeny set forth above and beginning with *Enzo Biochem II*. In particular, the application describes the actual nucleotide sequence of an exemplary set of 146 IBD genes because it sets forth for each gene in Table 1 a Genbank accession number for the deposited sequence. As held in *Enzo Biochem II*, these sequences and complementary probes that hybridize to them are adequately described. Additionally, the application expressly describes exemplary sizes and percent identity of probes that can be used in the claimed method of detecting differential expression of at least 5 different genes shown in Table 1. Accordingly, the application sufficiently describes the IBD genes to be detected as well as the probes that can be used and there is nothing hypothetical about the claimed method. Therefore, withdrawal of this ground of rejection is respectfully requested.

Rejections Under 35 U.S.C. § 103

Claims 5-7 and 19-29 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Alexander et al. in view of Puolakkainen et al. and Prehn et al. Alexander et al. is alleged to describe a method to determine altered expression of protooncogenes in IBD. The Office concedes that Alexander et al. do not describe the differential expression of at least 5 gene shown in Table 1. Puolakkainen et al. is alleged to describe expression profiles of stromelysin-2, collagenase and MMP-12 in intestinal ulcerations. Prehn et al. is cited as allegedly reporting a role for TNF-α, IL-18, IL-12, IL-10 and IL-4 in Crohn's disease. The Office concludes that the genes in Table 1 are well known for their role in IBD and that it would have been obvious to use all the known genes involved in IBD to determine the IBD or pre-IBD phenotype because the efficiency of the method improves.

Applicant claims a method for determining an IBD or pre-IBD phenotype of a test cell from a given tissue. The method includes detecting the presence or absence of differential expression of at least 5 different genes shown in Table 1 relative to a control cell of the given tissue. The claimed method is neither described or suggested in the cited art to Alexander et al. in view of Puolakkainen et al. and Prehn et al.

The Office asserts that the genes set forth in Table 1 "are well known for their role in IBD." Support for this conclusion appears to be that the exemplified IBD gene set is not novel because "the specification disclose[s] the Genbank accession numbers of the genes used in the claimed methods." Office Action at page 6, paragraph 2. However, such a generalized conclusion that the IBD genes shown in Table 1 are well known for their role in IBD is unsupported by the assertion that the genes are known. Rather, the application teaches that differential expression of at least 5 genes from Table 1 can be used to determine an IBD or pre-IBD phenotype. Absent Applicant's own disclosure, the Office fails to provide a showing that at least 5 of the genes in Table 1 have a "role" in IBD or that at least 5 of the genes in Table 1 are differentially expressed.

To establish a *prima facie* case of obviousness, the Office must show that the prior art would have suggested the claimed invention to one of ordinary skill in the art and that it could have been carried out with a reasonable likelihood of success when viewed in the light of the prior art. *Brown & Williamson Tobacco v. Philip Morris*, 229 F.3d 1120, 1124 (Fed. Cir. 2000). The first prong of

this test is unsatisfied because the Office simply asserts that a person skilled in the art would have been motivated to use all known genes involved in IBD "because the efficiency of the method improves (ie, [the] more markers used the more different mechanisms involved in IBD are determined)." Office Action at page 7, lines 2-5 (emphasis added). However, there has been no showing that such a general conclusion is supported by the cited art, particularly in light of the omission of cited language from Alexander et al., Puolakkainen et al. and Prehn et al. by the Office.

Establishing that the prior art would have suggested the claimed invention requires an underlying factual showing of a suggestion, teaching, or motivation to combine the prior art references and is an "essential evidentiary component of an obviousness holding." *Brown & Williamson Tobacco*, 229 F.3d at 1124-25 (*quoting C.R. Bard, Inc. v. M3 Sys., Inc.*, 157 F.3d 1340, 1351-52 (Fed.Cir.1998); *see also C.R. Bard* at 1351 (obviousness requires some suggestion, motivation, or teaching in the prior art where to select the components that the inventor selected and use them to make the new device); *In re Kotzab*, 217 F.3d 1365, 1370 (Fed. Cir. 2000) (there must be some motivation, suggestion or teaching in the prior art of the desirability of making the specific combination that was made by the applicant). The evidentiary showing must be clear and particular and broad conclusory statements about the teachings of the cited references, standing alone, are not "evidence." *Brown & Williamson Tobacco*, 229 F.3d at 1125 (*quoting In re Dembiczak*, 175 F.3d 994, 1000 (Fed.Cir.1999), abrogated on other grounds by *In re Gartside*, 203 F.3d 1305, 53 USPQ2d 1769 (Fed.Cir.2000)).

One purpose of the evidentiary requirement for showing a suggestion, motivation or teaching of the claimed combination is to prevent impermissible hindsight reconstruction of the claimed invention based on Applicant's own disclosure. *C.R. Bard*, 157 F.3d at 1352; *In re Dembiczak*, 175 F.3d 994, 999 ("[c]ombining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability - the essence of hindsight").

Applicant respectfully submits that the Office has not provided a factual basis for its conclusions. The Office has failed to show that it would have been obvious to one of ordinary skill in the art to have modified the method of Alexander et al. with the genes of Puolakkainen et al. and Prehn et al. to obtain the invention claiming detecting the presence or absence of differential

expression of at least 5 different genes shown in Table 1. First, it is Applicant's disclosure that teaches that the detection of the presence or absence of at least 5 genes from Table 1 is determinative of IBD or pre-IBD. The Office fails to show that Alexander et al., Puolakkainen et al. and Prehn et al., alone or in combination, describe at least 5 differentially expressed genes from Table 1 that are present or absent in IBD or in pre-IBD. Second, the Office also has not pointed to particular language in any of Alexander et al., Puolakkainen et al. or Prehn et al. to support improved efficiency of the claimed method when "all" known genes involved in IBD are screened. Third, the Office's conclusion incorrectly focuses determination of "different mechanisms" rather than determination of IBD or pre-IBD as claimed.

The required evidentiary showing, pointing to some motivation, suggestion or teaching in the prior art of the desirability of making the specific modification, in particular, the detection of the presence or absence of at least 5 differentially expressed genes shown in Table 1 is lacking from the assertions in the Office Action. While the Office provides that "the efficiency of the method improves" or that more markers can determine "different mechanisms" as providing the motivation for providing the missing element of "the presence or absence of differential expression . . . of at least 5 different genes shown in Table 1," the federal case law requires that the evidentiary showing be clear and particular and does not allow for broad conclusory statements about the teachings of the cited references. Absent such evidence, the Office is impermissibility relying on hindsight. Accordingly, the cited art to Alexander et al., Puolakkainen et al. and Prehn et al. fail to teach, suggest or provide a motivation for one skilled in the art to carry out the claimed invention with a reasonable expectation of success.

In light of the remarks above, Applicant contends that the claimed invention is unobvious over the cited art. Accordingly, Applicant respectfully requests withdrawal of the rejection under § 103 over Alexander et al., Puolakkainen et al. and Prehn et al.

Claims 5-7 and 19-29 also stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Dieckgraefe et al. in view of the specification. The Office alleges that Dieckgraefe et al. describe a method for identifying genes exhibiting changes in expression in IBD, but concedes that Dieckgraefe et al. do not recite the genes or probes used in the claimed method. However, the Office alleges that Applicant argues that the genes in Table 1 are well known in the art as markers

of IBD or involved in IBD. The Office concludes that it would have been obvious to use the method of Dieckgraefe et al. and the known genes recited in Table 1 because those skilled in the art would have been motivated to use these well known to as markers of IBD or involved in IBD.

As with the § 103 rejection over Alexander et al. in view of Puolakkainen et al. and Prehn et al., this rejection similarly fails to provide an underlying factual showing that it would have been obvious to one of ordinary skill in the art to have modified the method of Dieckgraefe et al. with at least 5 different genes shown in Table 1 to obtain the claimed invention. Applicant clarifies for the record that it is not aware of any admission absent Applicant's own disclosure, nor does Applicant now concede, that the genes described in Table 1 were well known in the art as markers of IBD or involved in IBD or play a role in IBD at the time the application was filed.

The federal precedent is clear that use Applicant's own disclosure as a blueprint for arriving at the claimed invention is impermissible absent clear and particular evidence in the prior art of a suggestion, teaching or motivation to obtain the claimed invention. *C.R. Bard*, 157 F.3d at 1352; *In re Dembiczak*, 175 F.3d at 999; *Brown & Williamson Tobacco*, 229 F.3d at 1124-25; *accord Uniroyal, Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044, 1051-52 (Fed.Cir.1988) (it is impermissible to reconstruct the claimed invention from selected pieces of prior art absent some suggestion, teaching, or motivation in the prior art to do so); *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143 (Fed.Cir.1985) (it is insufficient to select from the prior art the separate components of the inventor's combination, using the blueprint supplied by the inventor).

The broad conclusory statements made in the Office Action that the genes in Table 1 are well known in the art as markers of IBD or involved in IBD or play a role in IBD are unsupported by any evidence in the cited art to Dieckgraefe et al. Further, the assertion that such genes in Table 1 are known similarly fails to provide a suggestion, teaching, or motivation to arrive at any of at least 5 different genes in Table 1 whose presence or absence of differential expression is determinative of IBD or pre-IBD. Further, use of Applicant's disclosure for such a teaching is impermissible absent clear and particular evidence in the cited art, which is lacking in Dieckgraefe et al. Therefore, the required evidentiary showing, pointing to some motivation, suggestion or teaching in the prior art for making the specific modification, in particular, at least 5 different genes shown in Table 1, that was made by the inventor is lacking from the assertions in the Office Action.

Absent such a showing, the rejection over Dieckgraefe et al. constitutes an improper hindsight reconstruction based on Applicant's own disclosure. Therefore, Applicant respectfully requests withdrawal of this ground of rejection.

CONCLUSION

In light of the Remarks herein, Applicant submits that the claims are in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, he is invited to call the undersigned attorney.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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